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THE UNIVERSITY OF TEXAS, SCHOOL OF MEDICINE
GALVESTON

THE MEDICAL EDUCATION OF THE EIGHTH SERVICE COMMAND, U. S. ARMY

W. Lee Hart*

It is with mixed emotions of humility and pride that I enter the circle founded by that great humanist, William Webster Root, who had alertness to mankind, vitality of feeling, and human understanding. My humility comes from a knowledge of my own shortcomings and pride that my confreres have found me "worthy to serve the suffering."

The Medical Educational Program of the Eighth Service Command has been a remarkable experiment in postgraduate medical training, and as such merits description.

With the expansion of the Army during the present emergency, the Medical Department was increased to an unprecedented size to meet the needs of the Forces. From necessity Medical Department personnel who were called to active duty had to be immediately assigned and few could be given special training. This Headquarters realized the necessity of inaugurating a program of medical education of such proportion and so co-ordinated in professional and military preventive medicine as to attain an adequate and efficient care of the sick soldier and the preservation of the health of every soldier. The fixed policy was that the medical personnel should receive instruction in their own environment and in relation to their own problems.

In accord with this policy a program was initiated at all stations. This method of medical training encompassed the well trained and less well trained while actually performing their assigned duties. The immediate problem was in the field of preventive medicine with special reference to venereal disease control and to sanitation. A program was carried out with the able assistance of Colonel Knox Miller of the U. S. Public Health Service who was assigned to our Headquarters

*Chief Surgeon, Eighth Service Command. This address was given under the auspices of Alpha Omega Alpha, National Honorary Medical Society, in Randall Hall, The University of Texas Medical Branch, Galveston, August 24, 1944, when Colonel Hart was made an honorary member of the Society.

as Liaison Officer. We obtained effective co-operation with the health authorities of the states composing the Service Command. The educational program was based largely on epidemiological considerations. It developed in the recognition of the situation that in the field of preventive medicine military installations and the surrounding civilian community are inseparable.

With the assignment of a consultant in nutrition, a most comprehensive educational program was developed which resulted in educating the mess personnel in the difference between nutrition and food—that one might get plenty of food and not necessarily be well nourished—and in the proper handling and preparation of food so as to preserve the maximum amount of nutrients. The program also educated the individual as to what he should eat and be benefited insofar as his health is concerned. In this we have been most successful.

With the assignment of a consultant in industrial medicine, a very intensive educational program was entered into for Medical Department officers, administrative officials, and industrial workers in the prevention of disability. The decrease in accidents graphically shows the result of this program. We have prepared a manual, "Toxicology and Prevention of Industrial Diseases," which is now in its third edition and which has received high praise throughout the country from those engaged in industrial work.

Later consultants in surgery, medicine, neuropsychiatry, radiology, and orthopedics were assigned. The educational programs which consisted of ward rounds, journal clubs, individual and combined staff meetings, and demonstration of autopsies, were augmented by the visits of the consultants. It was understood that the consultants would develop the existing educational program and would do their teaching on the wards and on the cases that were actually there. The educational program was further augmented by wartime graduate medical meetings at hospitals in this Service Command. These sessions were received favorably by the medical officers, and resulted in much stimulus. Under the frequently boring conditions of routine medical practice at a military post, it is

essential to offer every opportunity to keep abreast of current advances and to maintain interest in them.

This Headquarters obtained a grant from the Rockefeller Foundation to be used for medical educational purposes, whereby medical installations could be visited by eminent specialists and educational material furnished to further the development of the program. To stimulate interest and keep the medical officers informed, arrangements were made with the Massachusetts General Hospital to furnish clinicopathological material on selected cases, complete with case histories, differential diagnoses, clinical and pathological discussions supported by slide reproductions and photomicrographs. The clinicopathological material is distributed to all stations in this Service Command. It was felt that the clinicopathological material would be most valuable to the smaller hospitals which have a limited amount of appropriate clinical material at hand.

We early realized the importance and seriousness of the problems of the medical service in its regard to neuropsychiatry. Available reprints on this subject were obtained and are continually being distributed to the field. In addition, major clinical cases of psychosis, psychoneurosis, and psychosomatic or neurological disorders are chosen by the Neuropsychiatric Consultant from those submitted by the hospitals in this Command. These are worked up for distribution and study. One of the most important and valuable parts of the medical educational program is the system by which all autopsy protocols of deaths in this Service Command are submitted to this Headquarters for review and comments, which are returned to the station or general hospital concerned.

Arrangements were made whereby invitations were extended to a number of nationally known physicians, specialists in their fields, to visit medical installations of this Command. They accepted this invitation and many have visited our installations. Invitations were extended to Deans of Medical Schools in this Service Command inviting them to participate in the educational program. The University of Texas and Tulane accepted and submitted a list of their teaching staffs they would make available. These experienced medical teachers have been

of great assistance in the program. Other schools signified their intention of accepting as soon as conditions warranted. The staffs of these medical schools conducted clinics, bedside conferences, and lectures at stations in this Service Command. We are deeply grateful for their help.

The program outlined has been co-ordinated so as not to interfere with the routine medical service that is required of hospitals. It has definitely improved the medical service by the stimulus of the educational approach. Numerous enthusiastic letters have been received from medical officers evincing that the program has been of value to the staffs of the hospitals and frequently they request that more of them be conducted.

In connection with the educational program and with a view to systematizing and equipping libraries in all hospitals of the Command with a normal quota of books, adequate in number, kind, and quality, a careful study was conducted during the year by the consultants of this Headquarters in conjunction with the staffs of the medical installations, in an effort to determine just what constitutes the smallest library which will provide hospitals with the number of books sufficiently adequate to answer almost any question that would arise in caring for individuals suffering from most any type of disease. As a result of this study, our hospital libraries are now well equipped.

Due to the global aspect of the present war tropical diseases have become a major concern. We realized the necessity of all medical officers having a working knowledge of tropical diseases which will be encountered in increasing numbers within the zone of interior hospitals as well as in overseas assignments. A working knowledge of tropical diseases will be of definite value to the medical officer when he returns to civilian practice. The supply of clinicopathological conference material on tropical diseases already distributed are being enthusiastically received.

A high level of medical service in the Service Command has been maintained in spite of the frequent interruptions of our staffs due to sending key men to foreign duty by the co-operation of so many in our medical educational program.

In compliance with our insistency, the Rockefeller Founda-

tion sent Mr. George Gray to survey our educational program and afterwards sent Dr. Alan Gregg to advise with us as to its betterment. May I quote two paragraphs of Mr. Gray's report:

"The fact that the Army doctors see the visiting professors as intimately as they do has a stimulating effect. To brush shoulders with the leaders of their profession, to submit cases to these eminent authorities and get consultations, opinions, the give-and-take of discussion—here is an opportunity the like of which would come to few of them in private practice. In all, some thirty specialists have visited hospitals of the Eighth Service Command in the present program."

"In the list of appropriations made by the Foundation last year this grant for the Eighth Service Command does not loom particularly large. But in the light of its accomplishment one may question if ever any appropriation of like amount has served so many institutions, promoted so many branches of medical education, and touched the lives of so many individuals. Indeed, the project is unique in the breadth of its range. It is helping the Army, in this largest of the Service Commands, to provide better military medical service—and when these doctors return to civil practice the benefits of their wartime medical education will continue to serve the postwar world."

SURVEY OF THE ARTHROPOD-BORNE VIRUS ENCEPHALITIDES IN TEXAS WITH PARTICULAR REFERENCE TO THE LOWER RIO GRANDE VALLEY IN 1942*

W. McD. Hammon, W. C. Reeves, and J. V. Irons

In 1941, evidence was acquired based on serological and epidemiological investigations indicating that Eastern equine, Western equine, and St. Louis encephalitis viruses were infecting man and domestic animals in the lower Rio Grande Valley, Texas (Hammon, 1941, 1943; Bohls and Irons, 1942). These are the first reports of the probable concurrent activity of these three types of virus in a single area. The probable cases of human infection with the Eastern type virus are the only cases reported in man since the 1938 epidemic in Massachusetts (Feemster, 1938; Fothergill, Dingle, Farber, and Connerly, 1938; and Webster and Wright, 1938). The Texas epidemic began in May, 1941, following an epizootic of equine encephalomyelitis which occurred during April in nonvaccinated horses on the Boca Chica flats, southeast of Brownsville. Eastern equine virus was repeatedly isolated from horse brains (Randall and Eichorn, 1941; Mohler, 1941; Bohls and Irons, 1942). Several isolations of the Western type virus were also made (Mohler, 1941).

The year following the 1941 outbreak, plans were made for a co-operative investigation in the Lower Rio Grande Valley by the Texas State Health Department and the Hooper Foundation, University of California, San Francisco. There appeared to be a strong possibility that at least a few cases might occur in horses or man in this area in 1942, since it was an irrigated region with sustained high temperatures; so during April, May,

*From the George Williams Hooper Foundation for Medical Research, University of California, San Francisco, and The Texas State Health Department, Austin, Texas. This investigation was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and the University of California. Aided by a grant from the National Foundation for Infantile Paralysis. Received for publication September 10, 1944.

and June entomological and serological surveys were made in the vicinity of San Benito, Cameron County, and serological surveys were made during the summer in numerous other areas of the State. Unfortunately, for the result of these surveys, the expected cases of infection did not occur. Despite the failure to observe apparent disease, the studies were continued as planned since there appeared to be a possibility of discovering an inapparent reservoir or enzootic state.

Entomological Studies in Cameron County

A total of 22,768 mosquitoes representing 6 genera and 19 species were tested for virus content by mouse inoculation (Table 1). No virus isolations were made. Due to a severe drought (record for 20 years) catches were lower than anticipated, especially for certain species [present occasionally at least in higher proportion, as reported by Fisk and LeVan, 1941], namely *Culex tarsalis Coq.* (60 specimens), which is an

TABLE 1

Mosquitoes Collected in the Lower Rio Grande Valley of Texas, 1942, and the Results of Tests for Virus Content

Mosquito Species	No. Tested	Viruses Isolated
Culex tarsalis	60	0
Culex erraticus	13,466	0
Culex quinquefasciatus	2,973	0
Culex salinarius	315	0
Culex coronator	434	0
Anopheles pseudopunctipennis	101	0
Anopheles crucians	178	0
Anopheles quadrimaculatus	1,531	0
Aedes scapularis	230	0
Aedes taeniorhynchus	380	0
Aedes sollicitans	13	0
Aedes vexans	136	0
Mansonia titillans	647	0
Psorophora cyanescens	502	0
Psorophora signipennis	9	0
Psorophora ciliata	250	0
Psorophora discolor	457	0
Psorophora confinnis	1,026	0
Deinocerites spanius	60	0
Total	22,768	0

important vector of encephalitis elsewhere* and *Aedes aegypti* (Linnaeus) (none) the probable vector of dengue fever in this area. Irrigation water, due to the low flow of fresh water in the Rio Grande, in a region barely above sea level, contained an unusually high concentration of salts, possibly accounting for the absence of breeding of certain species common other years.

In the temporary field laboratory established at San Benito, experiments were made to test the ability of certain local mosquito species to act as vectors of the encephalitis viruses. In Table 2, a summary of certain of these experiments is presented. Complete protocols of all experiments have been presented elsewhere by Hammon and Reeves (1943 a, b). The first transmissions of St. Louis virus with *Culex tarsalis* and *Culex coronator* Dyar and Knab were accomplished at this time.

TABLE 2

Experimental Transmission Studies

Mosquito Species	St. Louis Virus		Western Equine Virus	
	Time Transmission Effected	Persistence of Virus in Mosquitoes	Time Transmission Effected	Persistence of Virus in Mosquitoes
Culex tarsalis	4–10 days*	15 days*	.....	.....
Culex coronator	8–10 days	11 days*	.....	.....
Culex quinquefasciatus	negative†	11 days*	.....	.....
Psorophora confinnis	.....	.....	negative	7 days*
Aedes taeniorhynchus	7 days	7 days	.....	.....

*Experiment terminated, not tested at a longer interval.

†Positive transmission experiments have since resulted from tests employing Southern California strains of *Culex quinquefasciatus*.

Entomological Studies in Travis County

In the late fall of 1942, 29 *Culex quinquefasciatus* Say and 13 *Aedes aegypti* were trapped on the premises where two horses died, supposedly from encephalomyelitis. Virus was not obtained by inoculation of equine brain suspensions into

**Culex tarsalis* has now been found infected with encephalitis viruses in Washington, California, and Nebraska (WMH and WCR).

laboratory mice, nor was virus obtained from suspensions of mosquito tissues tested in a similar manner.

Serological Studies in Cameron County

In Cameron County, 82 avian and 53 mammalian sera were taken to determine the incidence of neutralizing antibodies to the three types of encephalitis virus. None of the sera from animals born during 1942 had antibodies to any of the three encephalitis viruses under consideration (Table 3), yet of those animals born in 1941 (the year of the epizootic), a small number did have antibodies to one or more of the three viruses.

TABLE 3

Results of Neutralization Tests on the Sera of Texas Animals

Species	Western Equine Virus			St. Louis Virus			Eastern Equine Virus		
Cameron County	Pos.	Ques.	Neg.	Pos.	Ques.	Neg.	Pos.	Ques.	Neg.
Jack Daw	0	2	26	0	0	5	0	0	3
Mourning Dove	0	1	2	0	0	1	0	1	1
Chicken hatched 1941 or before	1	1	12	0	0	10	0	0	11
Chicken hatched 1942	0	0	7	0	0	14	0	0	16
Cow born 1941 or before	4	2	8	1	7	13	6	2	8
Calf born 1942	0	2	7	0	1	9	0	1	8
Pack Rat	0	1	8	0	1	5	0	0	4
Cottontail Rabbit	0	0	2	0	1	3	0	0	2
Total	5	9	72	1	10	60	6	4	53
Other Parts of Texas									
Chicken hatched 1941 or before	8	5	48	5	3	67	0	5	36
Chicken hatched 1942	2*	4	36	1	1	32	0	2	30
Turkey hatched 1941 or before	0	1	5	0	0	6	0	0	3
Turkey hatched 1942	0	0	4	0	1	5	0	0	2
Duck	0	0	2	0	0	3	0	0	2
Guinea Hen	0	0	2	0	0	1	0	0	2
Horse (unvaccinated)	7	1	4	1	1	10	4	1	6
Wild Rat	0	1	1	0	0	2	0	0	2
Total	17	12	102	7	6	126	4	8	83
Grand Total	22	21	174	8	16	186	10	12	136

*Because of insufficient serum these results could not be checked by repeating the test as is customarily done.

A series of 20 human bloods collected from Cameron County males of draft age included three with strong antibodies to St. Louis virus and one with a questionable titer. Of the 20, one had a questionable titer of Western equine antibodies and the rest were clear-cut negatives (Table 4).

TABLE 4

Neutralization Test Results on Human Blood Samples

	St. Louis Virus			Western Equine Virus			Eastern Equine Virus		
	Pos.	Ques.	Neg.	Pos.	Ques.	Neg.	Pos.	Ques.	Neg.
Cameron County Draftees									
Number Tested	3	1	16	0	1	19	....	....	....
Other Parts of Texas									
Number Tested	1*	1	14	0	1	15	0	1	11
Total	4	2	30	0	2	34	0	1	11

*A tentative diagnosis of "meningitis" had been made several weeks previously; in the spinal fluid cell count was relatively low and organisms were not found in smear or culture.

Serological Studies in Other Areas of Texas

A total of 302 bloods from domestic animals and birds were taken in various areas of Central or South Texas including Bastrop, Bee, Colorado, Calhoun, Kinney, Liberty, Uvalde, Travis, Williamson, Wilson, and Val Verde counties. A number of these bloods were tested for antibodies to Western equine, Eastern equine, and St. Louis viruses. The only antibodies found to Eastern equine or Western equine virus except in the horses (unvaccinated animals), were in chickens. These positives were all from chickens hatched in 1941 or before, with two exceptions in respect to the Western type virus, and because of insufficient sera these two positives could not be checked by retesting (Table 3). Antibodies to St. Louis virus were found in 7.1 per cent of the chickens hatched in 1941 or before, and in one chicken of the 1942 hatch.

DISCUSSION

The significance of the antibodies to Western equine and St. Louis viruses in domestic animals and man, has been rela-

tively well demonstrated by controls studied in areas where encephalitis has not been recognized (Hammon, Lundy, *et al.*, 1942; Howitt and Van Herick, 1942; and Hammon and Howitt, 1942). However, the question of the specificity of antibodies to Eastern equine virus in certain domestic animals has not been similarly established. In previous studies made by two of us (WMH and WCR) bloods from cattle and one horse taken in far Western areas, where the Eastern equine infection has never been recognized, have shown protection against the virus (Table 5), indicating, probably, a nonspecific reaction. However, other species tested from these areas supposedly free from Eastern type virus, have not shown any protection.

TABLE 5

Eastern Equine Neutralization Tests on Sera from Western Areas Where Eastern Equine Infection Is Not Recognized

Place and Animal	Pos.	Ques.	Neg.
Yakima, Washington, Horses	1	0	6
Nebraska, Horses	0	1	16
Yakima, Washington, Cows	8	1	4
Nebraska, Cows	4	2	5
Nevada, Calves	1	0	19
Nebraska, Chickens	0	0	27
Yakima, Washington, Ducks	0	1	5

A different picture was found in Texas in the incidence of serum antibodies in fowl to Western equine and St. Louis viruses, from that observed in previous studies made in Washington (Hammon, Lundy, *et al.*, 1942), and in California (Howitt and Van Herick, 1942). In the latter areas all evidence points to their incrimination as reservoirs of virus. In Texas, the relative absence of antibodies in domestic fowl hatched after the 1941 epizootic might well be correlated with the absence of apparent cases in man or horses, and the absence of virus in mosquitoes. This could be interpreted as an indication that either there was little or no infection in the area at the time of the study, or that any hypothetical inapparent infection was present principally in another reser-

voir, either vertebrate or arthropod, which was not included in the scope of these studies. It is possible that the paucity of *Culex tarsalis*, resulting probably from the unusual drought, accounted entirely for the absence of any indication of infection at the time of this survey. In the Yakima Valley it is the principal vector and all evidence points to domestic fowl as the principal temporary virus reservoir. We do not know enough about the persistence of antibody in the fowl's blood to interpret these data from Texas in regard to fowl which lived through the year of the epizootic, and then another season, without any infection (13.0 per cent positive to Western equine virus and 6.1 per cent positive to St. Louis virus).

Of those species of mosquitoes found by us in the Lower Rio Grande Valley of Texas during this survey or by Fisk and LeVan (1941), *Culex tarsalis*, *Culex coronator*, *Culex quinquefasciatus*, *Culiseta inornata* (Williston), *Aedes taeniorhynchus* (Wiedemann), and *Aedes vexans* (Meigen) are capable laboratory vectors of St. Louis virus as shown by Hammon and Reeves (1943 a). *Culex tarsalis*, *Culiseta inornata*, *Aedes aegypti*, *Aedes sollicitans* (Walker), and *Aedes vexans* are laboratory vectors of Western equine virus (Hammon, Reeves, Brookman, and Gjullin, 1942, and Hammon and Reeves, 1943 b). *Aedes aegypti*, *Aedes sollicitans*, *Aedes vexans* and *Aedes triseriatus* (Say) are laboratory vectors of Eastern equine virus (Davis, 1940). *Mansonia titillans*, present in large numbers, is the incriminated vector of Venezuelan type encephalomyelitis of horses and man. This virus just recently is reported to have spread to Trinidad (Gilyard, 1944).

Other blood sucking arthropods present in Texas have not been so completely tested in the laboratory. Records of the Texas State Health Department include notes on the presence of *Triatoma sanguisuga* (LeConte) which Grundmann, Kitselmann, Roderick, and Smith (1943) have suggested is a vector of Western equine encephalomyelitis in Kansas. *Dermacentor variabilis* (Say) which Blattner and Hays (1944) have shown capable of transmitting St. Louis encephalitis to mice and from generation to generation in the tick, is found over a considerable portion of Texas, according to Cooley (1938).

Summary

Data are presented from a study in Texas during 1942 of the arthropod-borne virus encephalitides. During the period of study in the areas surveyed with one or two possible exceptions, no cases of encephalitis were recognized in man or horse. Men and horses had apparently been infected the previous year with Eastern and Western equine and St. Louis viruses.

A total of 22,810 mosquitoes were tested for virus content with negative results. *Culex tarsalis*, the important vector elsewhere, was collected only in small numbers during the season when the survey was made, though reported previously as present in large numbers.

The vector ability of a number of mosquito species was tested and a summary is given of those species indigenous to the area of study, which are proven laboratory vectors of encephalitis.

A total of 249 avian, 68 mammalian, and 37 human sera were examined by means of the neutralization test for antibody against one or all of the three encephalitis viruses: St. Louis, Western equine, and Eastern equine types. The only antibodies found in animals born following the epidemic years were in three young chickens, one positive to St. Louis virus and the other two possibly positive to Western equine virus. Antibodies to all three viruses were found in the area of domestic mammals which had lived through at least one epizootic season, but only Western equine and St. Louis virus antibodies were found in fowl. Antibodies to St. Louis virus were found in four humans, one of whom had a suspicious illness a few weeks before the blood was drawn.

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THE COMPLICATIONS OF ANORECTAL SURGERY

JOHN McGIVNEY*

Rectal surgery has for years held an unenviable reputation for its postoperative pain and discomfort. Because of this reputation, much fear and apprehension is prevalent among the laity toward this type of surgery. To improve this outlook, we should endeavor to carry out proctologic surgery in such a manner as to secure for patients a maximum of postoperative comfort by obviating the complications which so frequently follow these operations. Formerly, it was thought that these complications were a part of the postoperative picture. However, this situation is now changed, for we now know that they are no longer justifiable.

Embarrassment may be spared the surgeon if he will make a thorough proctosigmoidoscopic examination, and insist upon a physical and routine laboratory examination of the patient before surgery. A barium enema cannot replace a proctoscopic examination, since the radiologist admits that it is not dependable in visualizing new growths in the middle and lower rectum.

At the Mayo Clinic, in a series of 1,072 cases of carcinoma of the rectum, some 49 per cent had been submitted to a recent anorectal operation for a condition not related to the new growth. Patients with blood dyscrasias or hepatic cirrhosis would probably be better off without anorectal surgery. It may be difficult to convince a tabetic patient that his loss of sphincter control is not a sequel of an anorectal operation, or that his neurogenic symptoms are not the aftermath of a spinal anesthesia. All of these situations should be dealt with before operation rather than as postoperative complications.

The complications which are most frequent following anorectal surgery are as follows:

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1. Excessive pain.
2. Postoperative hemorrhage.
3. Retention of urine.
4. Abdominal distension.
5. Abscess formation.
6. Rectal incontinence.
7. Anal stenosis.
8. Postoperative fissure.
9. Bridging over of a fistulectomy.
10. Thrombophlebitis and embolism.

Excessive Pain

The anorectal region is one of the most highly sensitive regions of the human body. The anus is richly supplied with sensory nerve fibers, and the region is surrounded in part by a thick, circular musculature which responds to trauma by a tetanic spasm. Because of these factors, it is impossible to completely obviate postoperative pain following operations in this area. However, if we observe certain principles of scientific surgery, this pain can certainly be reduced to a bare minimum. It has been said that good surgery must remove the abnormal tissues completely, with the least amount of trauma to the normal tissues, and to this might be added that it must relieve the symptoms of which the patient complains. Regarding hemorrhoidectomy, there are perhaps as many techniques as there are men who do them, and perhaps this is justly so, for each case offers an individual problem and to standardize the technique would certainly be unwise. However, we should select a technique which adheres closest to the established principles of surgery.

One of the common techniques is that of the clamp and cautery which has been used many years with varying success by many surgeons. It has simplicity in its favor, but apparently it does not remove the abnormal tissues completely for it is attended by many recurrences, and it is certainly not the least traumatizing procedure. The selection of an open, clean-cutting, non-burning, non-traumatizing type of operation, employing a minimum amount of ligature material, will

certainly obviate a great deal of postoperative pain for the patient.

A major factor in producing severe postoperative pain is the vicious and unnecessary practice of divulsing the external sphincter muscle. This practice is based upon the false premise that it prevents postoperative pain by producing a temporary paralysis of this muscle. Not only does it fail to accomplish this, but it produces damage to the muscle fibers and initiates intramuscular bleeding which greatly enhances postoperative pain and discomfort.

Another common cause of postoperative pain, is the practice of inserting a tube, drain or gauze pack in the anal canal following operation. If this is done, a rhythmical and painful contraction of the sphincter muscle results in its effort to expell this foreign body. A small rubber dam drain, which keeps the raw edges of the operative wound separated is all that is necessary for postoperative drainage, and this should be removed in twenty-four hours.

The sheet anchor in the treatment of postoperative pain following this type of surgery is the hot sitz bath. There is no reason why these should not be started on the first postoperative day and be continued throughout the patient's convalescence. They relieve pain, are cleansing to the operative wound, and stimulate healing.

For many years, there has been a constant search for some substance which when injected about the anus after operation, would cut off the pain impulses propagated from this area. Eucupin, nupercain, quinine and urea hydrochloride, procaine, benzocaine and diothane, alone or in combinations in oil, are some of those that have been tried with varying results. Perhaps the most recent is Morgan's solution which consists of procaine base, 1.5 per cent, butesin 6 per cent, benzol alcohol 5 per cent in sterile almond oil. These solutions at first were injected into the substance of the external sphincter muscle, but this procedure was objectionable in that it was attended by abscess formation in many instances, and it was thought that the wall of oil retarded healing of the operative wound. More recently, it has become the practice to inject the solution in the ischio-rectal space in a fanlike manner along the

course of the external hemorrhoidal nerves. In a fairly high percentage of cases, this method will produce some degree of postoperative analgesia of the area.

Postoperative Hemorrhage

This is one of the most distressing and troublesome of complications. In most instances the bleeding is slight and is easily controlled, but there are occasions when it is internal or concealed and may accumulate above the site of the operation. In this manner, a great volume of blood may be stored in the rectum, with no external evidence of bleeding, especially if the anus has been plugged postoperatively.

Postoperative hemorrhage is of two types:

1. Immediate—within twenty-four hours after operation.
2. Secondary—later than twenty-four hours after operation.

In immediate hemorrhage, the operative technique is usually at fault. A bleeding vessel has been overlooked, or a ligature which has been too loosely applied has slipped. The straining, vomiting and retching which follow general anesthesia, sometimes precipitate this type of bleeding. The bleeding can usually be controlled by a pressure bandage, especially if it is external, but if the bleeding is severe and internal, it may become necessary to return the patient to the operating room, anesthetize the area, and ligate the bleeding vessel. It is a poor policy to rely upon the natural clotting powers of the patient's blood to stop bleeding of this type.

Secondary hemorrhage is the most distressing type, for it usually occurs after the patient has been sent home from the hospital, or even after the patient is ambulatory. Following hemorrhoidectomy, it is usually precipitated by the sloughing of the stump of the hemorrhoid, which has been removed. The ligature normally separates between the eighth and twelfth day after operation and if infection and trauma are superimposed at this time, secondary hemorrhage may result. The treatment of this type of hemorrhage is usually more difficult, for the bleeding usually comes from an extensive necrotic area above the anorectal line where the vessels cannot be ligated

individually. It usually becomes necessary to utilize a mass suture ligature in order to control the bleeding, or if this is not possible, a gauze pack is inserted and left in place from twenty-four to forty-eight hours.

At the conclusion of an anorectal operation, it is a good policy to remove the blood and clots from the rectum, so that these may not subsequently saturate the dressing and give the false impression of postoperative hemorrhage.

Retention of Urine

Urinary retention has the distinction of being one of the most common complications of anorectal surgery. Since the sphincter muscles of the anorectal region and that of the bladder are supplied by the same segment of the cord it is not surprising that irritation of one produces reflex spasm of the other. For this reason, this complication nearly always manifests itself in some degree during the first twenty-four to forty-eight hours following operation, and it is usually aggravated by a plug or a pack left in the anal canal. Many of the patients who come to anorectal surgery are elderly men who frequently have some degree of obstruction to the bladder neck, because of hypertrophy of the prostate. This added to the trauma of the operation often produces a degree of retention which is extremely refractory to treatment.

Dr. Louis Buie at the Mayo Clinic feels that this complication is largely psychological and that reassurance and constant attention at the bedside will accomplish a great deal in obviating it. In his experience, physician patients are the ones most susceptible to it. Usually they have their own ideas regarding the management of this difficulty and they begin to initiate their treatment several hours after operation. When the treatment fails, they usually become alarmed and demand catheterization immediately.

The treatment of this complication is aimed at breaking the reflex arc which produces the spasm of the bladder sphincter. Many drugs have been utilized in an effort to accomplish this, but apparently, they have met with little success. Pilocarpine, atropine, pitressin, syntropan, and many others have been used for this purpose. There is no reason why these patients

should not be allowed to stand by the bedside or to sit erect to facilitate emptying the bladder, and if this is not successful, a hot sitz bath may produce the necessary relaxation. If the patient is unable to void within eight or ten hours after the operation, and the bladder is distended, he should be catheterized, and all tubes and packing should be removed from the anal canal.

In some clinics it has become the practice to instill into the bladder one ounce of 0.5 per cent mercurochrome solution, immediately after anorectal operations. The rationale of this procedure being that the solution acts as an irritant to the bladder and aids in overcoming the spasm of the sphincter muscle.

Abdominal Distension

This complication, although it is not frequent in its occurrence, may add greatly to the patient's discomfort. It differs from the ordinary type of abdominal distension, where the peritoneum has been incised, in that there is no paralysis of the peristaltic movements of the bowel. The difficulty lies in the failure of the gas to be expelled because of the postoperative spasm of the external sphincter muscle. Because of this difficulty, the gas accumulates for the most part in the large bowel, usually on the second or third postoperative day and is a source of great annoyance to the patient. It is a mistake to allow an inexperienced hand to insert a tube, the caliber of an ordinary rectal tube at this time, for it is extremely painful, it is liable to produce hemorrhage, and it is usually expelled within a few minutes after it is inserted. On the other hand, if a well lubricated No. 18 French catheter is gently inserted and passed above the external sphincter muscle, the distension will be relieved in a short time.

Abscess Formation

Anorectal surgery is unique in the fact that the wound always becomes infected and healing is always by secondary intention. Fortunately, the tissues are possessed of a natural resistance to the ordinary types of organisms found in this

area. For some strange reason, anorectal surgery has always been considered dirty surgery and frequently it is not considered necessary to scrub the hands and arms, to mask the mouth and nose, or to wear a gown. In this manner, organisms not common to the area are introduced and frequently complicate the postoperative picture. It is thought by many men that the introduction of sutures in the anorectal area encourages postoperative abscess formation, for they act as foreign bodies in an infected field. The injection of oil anesthetics after operation, as described previously, has been a frequent cause of abscess formation. Perhaps the greatest single factor in the prevention of postoperative abscess formation is the construction of well-beveled drainage zones, extending out from the anal verge, following operations in this area. This provides one of the fundamental necessities in the prevention and treatment of infection—that of adequate drainage.

Rectal Incontinence

Loss of control of the bowel more frequently follows operations which involve cutting across the external sphincter muscle, than any other type of anorectal operation. Much can be done to obviate this complication by careful planning of the operation so as to observe certain fundamental principles of dealing with this muscle.

1. If it becomes necessary to divide the muscle, it should be incised at right angles to its fibers, so as to produce as little deformity as possible.
2. If there are two internal openings of fistulas extending under the external sphinster muscle, they should be divided separately at two different operations.
3. If the fistulectomy wound is wide and gaping, a ligature marker should be placed in the trans-sphincteric portion and this part of the fistula excised at a later date. This is done to prevent wide separation of the muscle.

The practice of packing and repacking a fistulectomy wound invariably leads to some degree of rectal incontinence, for the edges of the incised sphincter muscle are kept apart, resulting in the formation of a large block of scar tissue between its ends, and a very inefficient sphincter muscle. The origina'

packing which was inserted after the operation should be removed in thirty-six to forty-eight hours and under no circumstances should it be replaced.

Anal Stenosis

This complication usually results from the over zealous removal of tissue at operation in the anorectal area. It has been incorrectly referred to as rectal stricture, but in reality, the deformity is in the anal canal and not in the rectum. The walls of the anal canal are normally in close apposition, whereas, those of the rectum are widely separated. If too much skin is removed from the anal canal, a narrowing is likely to occur, and anal stenosis is the result. Stricture of the rectum following rectal operations rarely occurs, and then only in those instances where the mucus membrane of the rectum is allowed to retract and is replaced by fibrous tissue.

Those who do a complete dissection in an attempt to remove the diseased tissues of the rectum completely, are occasionally threatened with this complication, but it can nearly always be averted by digital dilitation of the anal canal, beginning on the sixth postoperative day, and continuing every other day until the threat has been removed.

This complication can further be avoided by discontinuing the postoperative use of petrolatum or agar by mouth after the first bowel movement, and adjusting the consistency of the stool, with one of the bulk forming agents, to produce a firm stool which serves as an effective dilator of the anal canal.

Postoperative Fissure

Postoperative fissure is only occasionally encountered and then usually in elderly or poorly nourished individuals. It is usually suggested when there is persistent bleeding and painful elimination after a reasonable postoperative time has elapsed. The treatment is usually that of regulation of the consistency of the stool, but if the fissure persists and becomes extensive, it may be necessary to excise it at a subsequent operation.

Bridging Over of a Fistulectomy

The postoperative care in fistula surgery is of tremendous importance, and no one is qualified to carry it out except the man who did the operation, or one who was present at the table. The operation should be planned so that the wound heals from within outward, for it is imperative to prevent bridging over of the wound by granulation tissue, if the operation is to be successful. Bridging over is further prevented by daily raking over the depth of the wound with the gloved finger, or with sterile applicators until healing has occurred.

Thrombophlebitis and Embolism

These complications, fortunately, are so rare in their occurrence that they are hardly worth mentioning but their consequences are so disastrous that they should be included here. The possibility of these complications, remote as it may be, should be considered in weighing the evidence in favor of a rectal operation.

It is not unusual to find patients with advanced hemorrhoids to have a certain amount of venous stasis in the lower extremities. All that is needed to precipitate a thrombosis of these veins, and possibly a subsequent embolism, is to place the patients in the stirrups for an hour. It would, perhaps, be better if these patients were operated in the Sims, or even better, in the inverted position.

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MICROBIAL ADAPTATION TO PENICILLIN*

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There is a certain cogency in the problem posed by the possibility that infections now amenable to the action of penicillin may show, in the future, a reversal of this response and fail to yield to its action. This is especially true of gonococcic infections with which this discussion is primarily interested. The experience gained from the use of the sulfonamides provides an adequate reason for apprehension. The effective results in the treatment of gonorrhea with these drugs have been reduced from 85 per cent of the patients treated to approximately 55 per cent, according to a recent statement of Greenblatt and Street.

The phenomenon of increasing resistance of this disease to treatment has been generally observed. At The University of Texas where the problem of sulfonamide-resistance has been studied by Lankford and his co-workers in the gynecology clinic, an increasing incidence of strains of the gonococcus resistant to sulfathiazole has been observed during the period from 1942 to 1944. During the first ten months of this interval, the incidence of resistant strains isolated from the Negro female has increased from 21 to 36 per cent, and in the white female from 58 to 65 per cent. Should this trend continue, a situation may soon arise, if it has not already arisen, in which the usefulness of the sulfonamides in the treatment of gonorrhea will have been seriously impaired.

The mechanism by which resistance of the gonococcus is increased to sulfonamide is not known. It seems not unlikely from the observation of Lankford that the process may be dependent upon the survival of naturally occurring resistant variants. The increase in resistance has been found independent of the dosage of the drug, and has been observed to increase in some instances from 10 to 1,000-fold following an unsuccessful course of treatment. Although the loss of re-

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sistance is sometimes reversible and the organism may again exhibit sensitivity to the drug, the present position in the treatment of gonorrhea with the sulfonamides remains precarious.

In view of this experience with the sulfonamides, it is only reasonable that the question should arise of the possibility of a similar adaptation of the gonococcus, and of other micro-organisms, to the action of penicillin. It is with this particular aspect of the subject that I wish to deal.

Selective Action of Penicillin. The selective action of penicillin on micro-organisms was first studied by Fleming, the discoverer of penicillin, who found that the agent was effective in inhibiting the growth of staphylococci, streptococci, gonococci, meningococci, and *Corynebacterium diphtheriae.* These observations were confirmed and later extended by Florey and his associates working at Oxford University in England. In general, it has been found that penicillin is effective against gram-positive organisms, aerobic or anaerobic, and relatively feeble in its action against gram-negative organisms. However, within the limits of this generality both groups of organisms are known to manifest a wide variation in sensitivity to the agent. The bacterial potency of penicillin appears to be approximately equivalent to that of the other antibiotics and is of a magnitude of approximately 1,000 times that of the sulfonamides.

In connection with the venereal diseases in which the action of penicillin has been studied, it has recently been shown by Dunham and her co-workers that relatively high concentrations of penicillin, of from 800 to 1,000 Oxford units per 0.8 ml., definitely affected the motility of *Treponema pallidum* as determined by *in vitro* studies of organisms recovered from testicular lesions of the experimentally infected rabbit.

Clinical Observations. The clinical efficacy of penicillin on human infections with sulfonamide-resistant gonorrhea was first observed by Mahoney and by Herrell and their associates in 1943. During the short period of time since these original observations, penicillin has been used for the treatment of patients manifesting gonococcal infections resistant

to the sulfonamides, especially among the members of the military forces. The experience of the Army with this drug has but recently been described by Sternberg and Turner in a report on 1,686 cases treated in certain designated military hospitals. The effect of penicillin was such as to cause a disappearance of clinical signs and symptoms and a reversal of the bacteriological findings within 48 hours after treatment. A course of treatment with 160,000 units of penicillin achieved a cure in 98 per cent of the cases. Smaller doses of from 80,000 to 120,000 Oxford units were about as effective and gave satisfactory results in 96 per cent of the cases. It was found that an additional course of treatment raised the total successes to 99 per cent. It is worth noting that in no case was the infection resistant to penicillin. The failures in treatment were to be attributed apparently to causes other than a penicillin-resistant strain of the gonococcus.

In the United States Navy the treatment of sulfonamide-resistant patients has been more extensive than in the Army. Schwartz and Edge have presented the cumulative experience of this organization in the use of penicillin in 4,438 patients. Treatment was successful with the first course of penicillin in 95.9 per cent of those treated. On re-treatment of the 141 patients in whom the first course of therapy had been inadequate, failure to cure the disease was seen in only two cases. The criterion by which failure was judged was not stated. The optimal dosage of penicillin was considered to be in the neighborhood of 100,000 Oxford units administered in five doses, one every three hours.

The results thus far described have been concerned with the treatment of men. Although the use of the drug has not been so extensive in the treatment of women, the reports available are such as to indicate that penicillin is effective in sulfonamide-resistant patients of this sex. Differences in the anatomy of the genito-urinary structures with the attendant peculiarities of localization of the disease in the female offer certain barriers to the action of penicillin which do not obtain in the male patient. This is particularly true when the infection has extended into the fallopian tubes and there has given rise to tubal abscesses and to a chronic pathological process

in other pelvic tissues. The report of Cohn and others was the first to deal with penicillin in the treatment of gonorrhea in women. The results of treatment in 44 cases where infection had been resistant to the action of a sulfonamide were described. Of these patients, 15 had involvement of the adnexa. The average duration of infection was 92.5 days. From 50,000 to 100,000 Oxford units of penicillin were administered to each patient over a period of six hours, with the result that bacteriological reversal occurred in 43 instances within 12 hours after the termination of treatment. All of the patients were considered cured.

The warning of Greenblatt and Street with relation to the size of the dose administered to such patients should be heeded. It was their opinion that no attempt should be made to reduce the dosage to a minimal level but that it should be maintained at levels sufficiently high to assure the most satisfactory results. To achieve this, it was recommended that a total dosage of 150,000 Oxford units be employed.

Greenblatt and Street treated a total of 109 cases of sulfonamide-resistant gonorrhea in women. They, too, found that the symptoms of infection were abated within 24 to 48 hours following treatment, and that cultures for the gonoccoccus usually became negative within 12 to 24 hours following therapy.

Although the number of female patients treated at The University of Texas is small, 14 in number, certain observations (by Weaver, Cooke, and Lankford) concerning them are of some interest. The cases studied may be divided into two categories. In the first were patients whose infections were caused by a gonococcus resistant to sulfathiazole. In the second category were included those patients who had manifested repeated recurrences of the disease regardless of whether the strain of the gonococcus isolated was resistant to sulfonamide or sensitive to it. Of the six patients in the latter group, all except one had a chronic pelvic inflammatory disease. All patients developing recurrences following penicillin therapy were in this group. Four of the six recurrences appeared coincident with the second menstrual period after the patients had been discharged from the hospital where they were under

bacteriologic observation for a period of 30 days. Three of the six denied having had sexual contact after leaving the hospital. It seems reasonable, therefore, to assume that the reappearance of positive cultures was indicative of a relapse and not of a reinfection. It is of interest to note that four of the six patients who subsequently proved to be bacteriologically positive had received a minimal dose of penicillin, namely, 50,000 Oxford units. The dosage employed in the study was from 50,000 to 100,000 Oxford units of penicillin administered in amounts of 10,000 units every three hours. All of the patients treated showed a bacteriological reversal during the period of treatment.

Lankford studied the penicillin-tolerance of the gonococci isolated from the patients who subsequently returned with recurrences and found that in all cases the organism was sensitive to penicillin. The highest penicillin-tolerance of the strains which he tested was 0.02 Oxford units per ml. The most sensitive strain of staphylococci which he has studied had a tolerance of 0.04 Oxford units per ml. This may be taken as a measure of the relative sensitivity of the two organisms.

It was the impression from the observations on this small sample of patients that the dosage of penicillin employed was inadequate, especially in the presence of the more chronic and deep-seated localization of the infection in the pelvic tissues. It is probable that tubal abscesses containing viable gonococci were not sterilized by the amount of penicillin administered. It remains to be seen whether larger amounts of the drug would be effective in the treatment of lesions of this character.

Mode of Action of Penicillin. Penicillin acts either as a bactericidal or bacteriostatic agent, and it appears that no detectable amount of the substance is absorbed or destroyed in the process of bacterial inhibition. It is most active in its bactericidal properties when the infecting organisms are in a phase of active growth.

Penicillin is inhibited by a substance which is found in organisms resistant to its action and not in organisms sensitive to it. Abraham and Chain found, in 1940, an agent in *Escherichia coli* which destroyed penicillin and which they

called penicillinase because of its resemblance to an enzyme. Bacteria producing penicillinase are widely distributed in nature but are most commonly found among the gram-negative bacilli which inhabit the gastro-intestinal tract. Except for the Shigella group of micro-organisms, they are not primarily pathogens. It is not known whether penicillinase inhibits the action of penicillin much as para-aminobenzoic acid inhibits the action of the sulfonamides. In the case of *Staphylococcus aureus*, an increased resistance to sulfonamide is associated with an increased synthesis of para-aminobenzoic acid.

Kirby has extracted a highly potent penicillin inactivator from strains of staphylococcus, all of which were naturally resistant to penicillin. He was unable to find an inactivator in strains of this organism which were sensitive to the action of penicillin. Bondi and Dietz were not able to demonstrate a significant correlation between penicillin sensitivity and penicillinase production; although it was found that those organisms which produce penicillinase were not highly sensitive to penicillin. The development of resistance to the drug was not associated with the production of this inhibitor. The role penicillinase may have to play in determining the sensitivity of micro-organisms to penicillin cannot, therefore, be stated with certainty at the present time.

Adaptation of Micro-Organisms to Penicillin. Several workers have succeeded in developing penicillin-resistant strains of bacteria by cultivation in increasing concentrations of penicillin over long periods of time. Abraham and his associates (1941) were able to increase the resistance to penicillin of a strain of *Staphylococcus aureus* 1,000-fold by subculturing the organisms for a period of nine weeks.

In connection with the sensitivity of *Treponema pallidum* to penicillin, it is of interest to observe that Dunham and her co-workers have found that a strain of this organism obtained from an insufficiently treated rabbit with syphilitic infection was more resistant to the action of penicillin than was the strain originally. This, they thought, should be considered in the treatment of human syphilis in that care should be taken to administer a sufficient quantity of penicillin to cure the patient rapidly.

Perhaps this admonition is of some significance in view of a recent observation which I have made in connection with the treatment of a patient in the seropositive, primary stage of syphilitic disease. In this instance, the presence of the organisms was studied at hourly intervals throughout the early period of treatment by darkfield examination of the chancre. Sixteen hours after the initiation of treatment, *Treponema pallidum* had disappeared from the exudate of the lesion, and for a period of eight hours thereafter none was found. At 24 hours after the beginning of treatment, many organisms were again found in the exudate from the chancre, and they continued to be present for a period of 10 hours, at the end of which time, that is to say, 34 hours after the initiation of treatment, they finally disappeared.

It is impossible to evaluate the significance of the observation inasmuch as very little is known of the life history of *Treponema pallidum*, but one is prompted to question the existence of variants of the organism which were more resistant than others to the action of penicillin but which were not sufficiently resistant to prevent their final inhibition. It seems altogether possible that had larger doses of the drug been administered initially that this phenomenon might not have occurred. It will be of considerable interest to observe the subsequent course of the disease in this patient as one might assume that because of the apparent resistance of the organisms to penicillin, relapse of the disease might be anticipated.

In this connection, it should be pointed out that very little is known of the behavior of *Treponema pallidum* in superficial lesions of early syphilis following the administration of any of the chemotherapeutic agents, either arsenical or antibiotic. Perhaps much might be learned if it were the practice to follow continuously over a suitable period of time the darkfield examination of lesions in which the organism is present. This might offer a means of evaluating the efficacy of the treatment insofar as the subsequent course of the infection in the individual is concerned.

Implications of Resistance to Penicillin. Even though the initial results in the treatment of gonorrhea with penicillin have been unusually promising, it is necessary to consider

thoughtfully the possibility that the gonococcus may behave in its reaction to penicillin in the same manner as it behaves toward the sulfonamides. This is not only true of gonococcal infections, but it is true of infections with other pathogenic organisms which have been shown to increase in their tolerance to these drugs. Lankford, in a yet unpublished statement, has expressed the desirability of determining whether or not natively resistant strains of the gonococcus occur, for if the incidence of such strains is found to be significant there would arise a problem of public health of considerable importance. As a susceptible type of the organism is eliminated through the use of penicillin, selection and spread of the variants of the gonococcus, resistant to penicillin, might occur creating a situation analogous to that now existing with respect to gonorrheal infections resistant to the sulfonamides. He has indicated that there is also the equally important point of the permanent acquisition of resistance of strains of the gonococcus surviving inadequate treatment with penicillin. In this case as in the case of natively resistant strains, strains with an acquired tolerance might be transmitted and selected in the same fashion and with the same undesirable results as with the naturally resistant type of gonococcus.

Penicillin-Tolerance of the Gonococcus. In view of the problem stated above, Lankford has undertaken a study of the cultures of gonococci isolated from female patients seen in the gynecology clinic of the John Sealy Hospital of The University of Texas. The results of the study of 203 freshly isolated cultures from 100 patients for their *in vitro* tolerance to penicillin is soon to be published. His observations are of interest in that they throw some light upon the native tolerance of the gonococcus as it was observed in a satisfactory sample of human infections, and affords a basis of comparison with the tolerance of the same strains to sulfathiazole. The relative position of the range of tolerance to the two therapeutic agents may be some indication of what is to be expected from the use of penicillin as it becomes more universal. The bacteriologic observations taken together with the reports on the clinical use of the drug indicate that a more hopeful attitude

toward the efficacy of penicillin may be taken than toward that of the sulfonamides.

It was found that the range of tolerance to penicillin was relatively narrow in that variation of the extremes of tolerance showed but an eight-fold difference (0.0025 — 0.02 Oxford units per ml.). This characteristic of the gonococcus in its behavior toward penicillin is in striking contrast to that of the same strains of organisms in their behavior toward sulfathiazole. The range of sulfathiazole tolerance was found to be very wide with a difference of the magnitude of 10,000 fold (0.001 — 10.0 mgm. per cent).

There are, as Lankford has stated, few criteria by which the gonococci may be classified as to their resistance or susceptibility to penicillin. Four strains with a tolerance to penicillin of 0.01 Oxford units per ml. and one strain with a tolerance of 0.015 Oxford units per ml. were isolated from patients who responded subsequently to treatment with penicillin. The highest tolerance observed was 0.02 Oxford units per ml. This is a significantly lower tolerance than that of penicillin-sensitive staphylococci which was 0.04 Oxford units per ml. From these findings, it seems reasonable to believe that strains of the gonococcus possessing a high natural resistance to penicillin occur but infrequently, if they occur at all.

There remains, however, the possibility that the gonococcus may acquire a relative resistance to penicillin following inadequate doses of the drug. The answer to this question must depend upon the collection of an adequate sample of cases in which the tolerance of the organisms after the administration of varying doses of penicillin has been studied.

To this end Lankford has tested the strains isolated from ten patients at intervals of three, six or nine hours after the initiation of treatment. He failed to observe any significant decrease in sensitivity to penicillin. Although he has not observed early recurrences of the infection following treatment, he has been able to obtain six strains from patients manifesting late recurrences of infection, and none of these showed an increase in penicillin-tolerance. It is, of course, necessary to remember that in some of these cases the recurring symp-

toms of the disease may have resulted from reinfection and not from relapse.

It has been suggested by Cohn and Seijo (1944) that sulfonamide-susceptible strains of the gonococcus are relatively more inhibited by penicillin than are sulfonamide-resistant strains, thus indicating a correlation between the tolerance of the organism to penicillin and to sulfonamides. Of the strains studied in Lankford's laboratory, this relation was not observed, and it is also noteworthy that in studies dealing with staphylococci (Spink), pneumococci (Powell), and streptococci (Florey and Jennings), there has been no demonstrable correlation of the behavior of these organisms toward penicillin and the sulfonamides.

There is considerable evidence that naturally resistant strains of the gonococcus have been selected by the gradual elimination of strains susceptible to sulfonamide, and, as a consequence of this selectivity and the survival of the fittest with respect to their tolerance of the drug, gonorrhea during the past few years has displayed an increasing tendency to resist the therapeutic action of the sulfonamide drugs.

The reasonableness of an assumption that certain strains of gonococci may become adapted in like manner to the action of penicillin lies in the fact that it has been demonstrated by Florey and Jennings that strains of the staphylococcus relatively resistant to penicillin occur with considerable frequency, and that the resistance of the staphylococcus may be increased to a considerable degree during the course of treatment with penicillin (Rammelkamp). The consequences of this native and acquired resistance to penicillin are to be seen in the number of staphylococcal infections which have failed to yield to treatment with penicillin.

Although it may be concluded both from the study of Lankford and of Cohn and Seijo (1943) that the existence of natively resistant strains of the gonococcus do not occur, at least with any frequency (neither of these workers has detected strains which have a penicillin-tolerance greater than 0.02 Oxford units per ml.), and that the range of tolerance is narrow, the possibility still exists that subsequent observations may reveal an acquired resistance to penicillin on the part of such organisms after they have been exposed to its influence.

Penicillin in Syphilis. What the ultimate position of penicillin may be as an effective agent in the treatment of syphilis remains to be seen. Studies of the action of the drug in patients in the primary and secondary stages of the disease are now in progress (Moore and associates), but it is not possible to evaluate with any finality the results that have been obtained. The initial effect of penicillin on the disappearance of spirochetes from the surface lesions, on the healing of lesions, and on the reversal of the serological reactions of the blood give hope that this may be an effective therapeutic agent against syphilis. Relapses have already been observed, both serological and clinical following administration of the drug, but there is, as yet, no reason to indicate that there may be resistant strains of *Treponema pallidum* as there are resistant strains of the gonococcus. The failure of treatment as manifested in the relapses observed is to be interpreted as resulting from the failure to give to the patient an adequate amount of penicillin.

There are individuals who possess syphilitic infections which are resistant to the arsenical drugs, but whether this is the result of an infection with organisms of high tolerance to the therapeutic agent is unknown. It is necessary to take into consideration in the interpretation of such failures the fact that the resistance of the host may play an equally, or even more, important part in the response to treatment than may the sensitivity of the infecting organisms. The problem of adaptation of *Treponema pallidum* either to the host or to the therapeutic agent is one on which there has been but little study due in the main to the lack of technics adequate to its investigation.

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HORMONAL THERAPY IN MANAGEMENT OF CARCINOMA OF THE PROSTATE

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In 1941, Huggins and others demonstrated that depression of androgenic hormonal influence by castration or administration of estrogens, in most instances, inhibits the active progression of carcinoma of the prostate. Administration of androgens provides stimulus to its growth. Urologists eagerly applied these observations to the management of a hitherto discouraging problem. Subsequent reports have generally supported the results of the earlier workers.

In the past two and one-half years, 27 patients with an established diagnosis of carcinoma of the prostate have received hormonal therapy in the John Sealy Hospital. Five others have refused it. One died postoperatively. Urinary obstruction required transurethral resection in twenty-two of those also treated by hormonal methods. In the remaining five, obstruction resulting in complete urinary retention or the presence of large amounts of residual urine was relieved by estrogen administration without operative interference. It is possible that the number in this latter group would have been larger had this observation been made earlier. Combined castration plus estrogen administration has been used most frequently to secure androgen depression.

Utilization of hormonal therapy is individualized. Because its inhibiting influence often seems to gradually decline, its application is now being deferred here until definite subjective symptoms result from metastatic lesions. Recently the trend has been to employ estrogen administration first and resort to intracapsular orchiectomy if and when failure of estrogens to control symptoms effectively is exhibited. Following castration, maintenance doses of stilbestrol are continued indefinitely because androgens are also produced in other locations.

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Stilbestrol dosage, adjusted to individual tolerance, is usually three to five milligrams daily by intramuscular injection or one to three milligrams daily by mouth.

Dizziness, nausea and vomiting, and painful enlargement of the breasts may be associated with estrogen administration. These undesirable side effects are transient and subside promptly when the drug is withdrawn or the dosage is adequately reduced. Loss of libido and potentia uniformly accompanies castration and estrogen administration. Refusals to accept this treatment are usually based upon these considerations, for most patients are loathe to part with their virility.

Improvement was apparent in 19 and no improvement in 8. The most dramatic demonstrations of the effectiveness of hormonal therapy occurred in patients who were cachectic with extensive metastatic involvement and at times were suffering intolerable pain or were considered moribund. In most of these the rapid clinical improvement manifested by relief of pain, increase in appetite and weight, a general sense of well being, and resumption of normal daily activity was little short of miraculous. In a few instances surgical relief of bladder neck obstruction was rendered unnecessary. A variable degree of regression in the primary growth has been observed, and palpable or visible lymphatic lesions usually became no longer discernible. In one patient there was complete urinary retention due to bladder neck obstruction and paraplegia due to pressure of a vertebral metastasis on the spinal cord. Following orchiectomy and administration of stilbestrol there was no retention of urine; sensation and some motor power was restored in the lower extremities. This status has continued since February 9, 1944. In another patient regression of skin metastases followed administration of stilbestrol. As yet there is no x-ray evidence in this series to indicate that withdrawal of androgenic influence will prevent the occurrence or progress of demonstrable skeletal metastases.

Although the palliative results have been gratifying despite indications that several of these patients have been greatly benefited, it seems regrettably clear that hormonal control is neither curative nor permanent in its effect. For in no instance has complete regression of the malignant lesions occurred.

Furthermore, after a variable period of time, unless death resulted from some intercurrent disease, there was often some recurrence of the symptoms with progression to death from carcinomatosis. It seems significant that only ten of this group of twenty-seven are still alive in this two and one-half year period.

True evaluation of hormonal control is difficult. Those who have had even moderate experience with carcinoma of the prostate are familiar with its possible capricious behavior. While its fatal outcome is still certain, its course is as unpredictable as a high-school girl's romances. Thus one of our hospital records reveals that a diagnosis of prostatic carcinoma was established twenty years before the patient died of this disease and that during the intervening time he apparently enjoyed good health. Improvement following transurethral resection of bladder neck obstruction alone has in many instances compared favorably with that obtained by hormonal therapy. Consequently, while it must be considered an important improvement in management of carcinoma of the prostate, hormonal therapy requires further study and appraisal.

Summary

Hormonal therapy is a valuable adjunct in management of carcinoma of the prostate. When effective, the result is palliative and temporary rather than curative. Some regression in the malignant lesions may be noted. Estrogens should be used first to neutralize androgenic activity. Castration may be reserved until necessary. Evaluation is difficult because of the inherent variation in behavior of carcinoma of the prostate.

Table 1

Distribution of Hormonal Treatment of 27 Patients with Carcinoma of the Prostate

By Castration Alone	1
By Stilbestrol Alone	8
Combined	18
Transurethral Resections	22

TABLE 2

Summary of Results Obtained with Hormonal Therapy in 27 Patients

Marked Improvement	12
Moderate Improvement	7
Slight or No Improvement	8
Metastases	
Skeletal	17
Other	11
Alive Now (September, 1944)	10
Dead Now	16
Unknown	1

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AN ANATOMICAL INVESTIGATION OF THE RETINO-PITUITARY REFLEX

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Introduction

Many species of animals present phenomena which indicate that light stimuli can alter the gonadotropic functions of the hypophysis. This is particularly true of the birds. A dormant avian gonad can be developed to a stage comparable to the gonad of a breeding bird by exposure to a few minutes of additional light each day. In the pigeon, a non-spontaneous ovulator, the sight of another bird or a mirror image of itself is sufficient stimulus to produce ovulation; however, the isolated bird will not ovulate (Brooks, 1940; Matthew, 1938).

Bissonnette (1938), in a summary of numerous experiments, concluded that the eyes are the sole receptors for the artificial light stimuli. These observations suggest a retino-pituitary reflex by which the impulses have been postulated to pass by way of the optic nerves and the hypothalamus to the pars distalis of the hypophysis.

In a comparative study of the innervation of the hypophysis (Drager, 1943), it was observed from silver preparations of the avian brain that a conspicuous number of nerve fibers were contained in the hypothalamico-hypophyseal fasciculus. The majority of these fibers took origin bilaterally from a large nucleus in the wall of the third ventricle and from a region dorsal to the optic chiasma. The latter suggests a possible direct optic pituitary nervous connection. In most species of animals no direct neural connection can be demonstrated between the optic tract and the hypophysis, although certain studies concerning pigmentation in the amphibians indicate a neural connection between the eye and the pituitary gland. Collins (1935) also believes that retino-pituitary connections exist in the guinea pig. Since silver preparations show nerve fibers of the hypothalamico-hypophyseal fasciculus arising

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from the proximity of the optic chiasma, the present study was designed to ascertain if a neural connection could be demonstrated between the eye and the hypophysis of the bird.

Materials and Methods

Approximately three weeks following the removal of the left eye of seven adult pigeons the birds were sacrificed and perfused with a mixture of equal parts of 5 per cent potassium dichromate and 20 per cent magnesium sulfate. Perfusion was best accomplished by injecting the fluid directly into the heart of the lightly anesthetized bird with a 50 cc. syringe. This method eliminated the difficulty of cannulating the small arteries of the pigeon and also was advantageous in that the beating heart facilitated the distribution of the perfusing fluid. Following perfusion the brain with hypophysis attached was removed and prepared according to the Swank-Davenport method of demonstrating degenerated myelinated nerve fibers (Swank and Davenport, 1935). After staining, the tissues were dehydrated, embedded in soft paraffin and sectioned at 50 micra. The sections of the best five brains were mounted in clarite and examined microscopically.

Observations

The left optic nerve showed considerable degeneration. At the chiasma a complete crossing of the fibers occurred. The degenerated fibers could be traced from the optic chiasma to the right tectum where they enveloped its surface. A bundle of fibers could also be traced into the region of the basal optic nuclei and the lateral geniculate body. Other fibers could be followed more dorsally toward the nucleus of the posterior commissure and region of the lateral and medial nuclei of the thalamus. Degenerating fibers could not be traced directly from the optic tract or chiasma into the hypothalamico-hypophyseal fasciculus. No detectable degeneration was present in the hypothalamico-hypophyseal fasciculus.

Discussion and Conclusions

Physiologically, a functional retino-anterior pituitary mechanism is generally accepted. On the other hand, anatomical

studies have as yet failed to demonstrate a neural pathway from the eye or the hypothalamus to the pars distalis of the avian hypophysis. Pyridine-silver and Bodian's activated protargol preparations show a large hypothalamico-hypophyseal nerve tract in the bird, but no nerve fibers can be traced from the fasciculus to the anterior lobe (Drager, 1944). Neural connections between the hypothalamico-hypophyseal fasciculus and the pars distalis are more easily studied in the bird than in most animal forms in that the anterior lobe is completely separated from the processes infundibuli except for a small strand of the intervening pars tuberalis. Should fibers pass from the fasciculus to the anterior lobe they could be readily demonstrated.

After the removal of one eye, no degenerating nerve fibers can be followed from the optic tract to the hypothalamico-hypophyseal fasciculus. The Swank-Davenport method stains only degenerating myelinated fiber. There still remains the possibility of a direct optico-posterior pituitary nerve pathway of non-myelinated fibers. This is highly problematic considering the abundance of myelinated fibers in the optic tract and the size of many of the fibers contained in the hypothalamico-hypophyseal fasciculi. Undoubtedly, the optic-hypophyseal reflex involves more than one neuron with synapse in the hypothalamus.

Nerve fibers of the hypothalamico-hypophyseal fasciculus pass to the pars tuberalis and posterior lobe and probably influence their secretory activities. However, neurological staining technics do not indicate that the avian pars distalis is functionally innervated. This conforms with the views of Loewi (1935) who is of the opinion that the anterior pituitary is not stimulated by nerves but by humoral agencies.

Summary

1. One eye was removed from adult pigeons. Three weeks following the operation the birds were sacrificed, perfused and prepared according to the Swank-Davenport method of demonstrating degenerated myelinated nerve fibers.

2. Microscopic examination of the preparations revealed pronounced degeneration of the severed optic nerve. Degen-

erated fibers could be traced to the various structures related to the optic system. No degenerated fibers could be traced from the optic tract into the hypothalamico-hypophyseal fasciculus. Degenerated fibers were not detected in the hypothalamico-hypophyseal fasciculus.

3. A direct unmyelinated optico-posterior pituitary nerve pathway or a pathway involving more than one neuron still remains a possibility.

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SPECIFICITY OF BULLIS FEVER RICKETTSIA

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In the previous studies of Bullis fever a pathogenic rickettsia was recovered from ticks *Amblyomma americanum* of Camp Bullis, Texas (Anigstein and Bader, 1943). Guinea pigs inoculated with this strain (BT_1) showed fevers of various types, frequently splenomegaly and almost constantly pneumonitis. The organism was demonstrated in tissues of infected guinea pigs and identified with that isolated by Livesay and Pollard (1943) from human Bullis fever. Guinea pigs convalescent from the infection with BT_1 proved immune to the infectious agent of human origin (BH). Consequently the tick *A. americanum* was established a vector of Bullis fever in nature.

Since its isolation the tick strain has been maintained in guinea pig transfers for 22 generations. Since March, 1944, when lyophile technique was applied lyophilized tissue is being mostly used for experimental infections. This material occasionally proved more virulent as compared with fresh tissues producing fevers of higher intensity and shortening the incubation period. Among pathological lesions scrotal swelling and the involvement of the tunica vaginalis of guinea pigs were occasionally observed. Otherwise, the clinical course of the infection in guinea pigs remained within the range of symptoms as previously reported (Anigstein and Bader, 1943).

The study of the human Bullis strain (BH) isolated by Livesay and Pollard (1943) was continued, the strain being kept in guinea pigs for 15 generations in this laboratory. The virulence of this strain in its lyophilized form is very variable as some guinea pigs failed to react completely while in other series definite fevers often followed by short relapses were observed. The examination of the organs of guinea pigs infected with either human or tick strain gave further evidence of the rickettsial nature of the causative agent. Rickettsiae

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were demonstrated in Giemsa stained sections of tunica vaginalis, kidneys, adrenals and in lungs. In the latter, rickettsiae are located in the peribronchial inflammatory foci mostly perivascular and also in the endothelium of the vessels.

These results were confronted with the observations of the Rocky Mountain Laboratory, Hamilton, Montana, and of the Eighth Service Command Laboratory, Fort Sam Houston, Texas, where investigations on Bullis fever were simultaneonsly in progress. First-hand information as to the progress of the work and technical methods were obtained by one of the reporters (L. A.) during his visit to the Rocky Mountain Laboratory in March, 1944. The frequent exchange of information and of research material as well as the personal contact established between the three units have greatly facilitated the progress of the present work.

The agent recovered in 1943 from the tick *Amblyomma americanum* (BT_1) was first compared with the strain of the same origin isolated by the Rocky Mountain Laboratory. Although the diseases produced in guinea pigs by these strains are very similar in symptomatology and pathology their immunologic characters proved to be different. The rickettsial agent isolated by the Rocky Mountain Laboratory from *Amblyomma americanum* of Camp Bullis immunizes guinea pigs against American Q fever, to which our agent does not show any relationship. This was shown by challenging guinea pigs convalescent from BT_1 infection with the tick strain of the Montana Laboratory as well as with the original Q fever rickettesiae.* Similar experiments were carried out by the Eighth Service Command Laboratory and gave no indication as to any relationship to American Q fever. Immunological tests were also made with the rickettsiae of spotted fever and tsutsugamushi (scrub typhus). No immunity was found in guinea pigs recovered from infection with BT_1 strain and reinoculated with these two rickettsioses. On the other hand, as previously reported the BT_1 strain corresponds immunologically to the rickettsia of human origin (BH) recovered by Livesay and Pollard (1943).

*The immunity tests were carried out by courtesy of Drs. R. R. Parker and E. A. Steinhaus, Hamilton, Montana.

On the basis of the above findings it was decided to test the specificity of the tick strain (BT,) as well as that of the human strain (BH) on human volunteers. This was justified inasmuch as the natural disease in man is mild as observed by Woodland, McDowell, and Richards (1943), who recorded only one fatal case among one thousand cases observed on Camp Bullis.

A series of experiments was carried out on human volunteers inoculated subcutaneously with BT_1 or with BH strain. This was carried out in collaboration with Dr. R. K. Blair (Houston, Texas) whose clinical observations are herewith briefly reported. A total of eight young and physically fit volunteers served for this purpose. Five of them were inoculated with the BH strain, the other three with BT_1 strain. Fresh or lyophilized tissues of infected guinea pigs were used. In addition to general symptoms, particular attention was paid to the blood picture and lymphonodes, since leukopenia and lymphadenopathy are most characteristic for Bullis fever. In one case of the BH series the total white cell count dropped after inoculation from 10,200 to 4,900 and 3,700 while in another volunteer inoculated with the tick strain the drop was from 9,450 to 4,900. The differential count showed in all cases shift to the left and a relative lymphocytosis of 40–50 per cent. None of the patients were seriously ill but those developing fever complained of severe headache, burning of eyes, photophobia and general malaise. Fever developed in four volunteers. In one of them inoculated with the BH strain the fever began after ten days of incubation showing an intermittent type and ranging between 99 and 100° F. After the first fever attack swelling of axiliary and inguinal lymphonodes developed, the glands became larger within the next two days. The generalized lymphadenopathy persisted during the ten days fever period and then gradually declined with the recovery of the patient.

Another volunteer developed five attacks of fever each of one day duration during his fourteen days of moderate sickness showing no other symptoms except for a leukopenia of 4,600. One of the three volunteers inoculated with the BT_1 strain developed fever ranging between 99 and 100° for the

first six days, then dropping to normal for another six days and finally rising again for the last five days of the disease. The lowest blood count was 5,800 white cells at the end of the second week. All patients recovered promptly without sequelae.

The comparison of the above experimental cases with the symptomatology of Bullis fever as described by Woodland, McDowell, and Richards (1943) shows in addition to general symptoms and febrile reactions several characteristics which strongly suggest that the syndrom experimentally produced in human corresponds to Bullis fever. The generalized lymphadenopathy and a marked leukopenia associated with neutropenia deserve particular attention.*

The studies on Bullis fever were continued through 1944 and conducted along two main lines: (1) the study of the Bullis fever rickettsia (BT_1) in animals, and (2) the recovery of new strains from ticks.

I. Previous experience gave ample evidence that the guinea pig is not the animal of choice for experimental Bullis fever. This could be judged by the irregular response to the infection which frequently runs a sub-clinical course, and also by the scanty appearance of the rickettsiae in the organs. Results were no better when white rats and Swiss mice were used although mice occasionally died when inoculated directly with tick suspension. Death usually occurred within three weeks with splenomegaly and pneumonitis, but in the subsequent passages mice ceased to react. The pathological lesions of transfer guinea pigs were also in the present studies most prominent in the lungs where discrete, petechial hemorrhages, scattered over the lung surface and in the deeper lung tissue were observed. These petechiae may coalesce to somewhat larger inflammatory foci. On sections intracellular bodies different in sizes and stained purple with Giemsa were observed. These bodies were previously interpreted by the reporters as aggregates of single elements (Anigstein and Bader, 1943, 403), which assumption has gained further confirmation by the present studies. The application of the Macchiavello stain,

*The clinical account of these experiments will be published separately by Dr. R. K. Blair.

which is specific for rickettsiae, was in this regard of particular value. Impression smears of lung and spleen tissues from guinea pigs infected either with the tick strain or the human agent showed intracytoplasmic round or irregularly shaped bodies which stained bright red. By location and appearance they can be compared with "inclusion bodies" as they occur in true virus infections. They were found most frequently in mononuclear and alveolar lung cells as well as in mononuclear cells and large lymphocytes of the spleen. They were found single or multiple in one cell. In addition to these "inclusion bodies" delicate, rod shaped red stained introcytoplasmic rickettsiae were present, showing the characteristic arrangement in palisades, short chains or clusters. In properly differentiated Macchiavello preparations the inclusions can be resolved into compact masses of organisms (coccoid or bacillary in shape). In other instances, these aggregations apparently broke into single organisms. These observations are of considerable interest as they correspond to the recent findings of English workers (Begg, Fulton, and van den Ende, 1944) on inclusion bodies in association with rickettsiae. These authors have observed a correlation between typhus rickettsiae and inclusion bodies in a resistant host (rabbit) whereas in a susceptible host (mouse) typical rickettsiae dominate. It is therefore highly probable that the inclusion bodies as they appear in Bullis fever in the relatively resistant guinea pig represent the dominant phase of the agent.*

II. Beginning with May, 1944, when the tick season in central Texas was almost in full swing, investigations of ticks from Camp Bullis were taken up again. This was made possible, thanks to the generous collaboration of the Eighth Service Command, particularly to the assistance of Dr. J. M. Brennan who supplied us with ticks. The ticks *(Amblyomma americanum)* were furnished in several lots, the total number of specimens being 1,850 (nymphs and adults).

The ticks were first soaked in a solution of merthiolate (1:1000) for several hours, then washed with saline plus 0.5 per cent glucose, triturated and centrifuged at low speed.

*Studies on this subject which may contribute to our concept of rickettsiae and viruses are initiated in this laboratory.

The supernatant was divided into portions: one portion was filtered through Berkefeld "N" and inoculated into eight guinea pigs intra-abdominally. The unfiltered portion was injected into another series of ten guinea pigs. After an incubation period from 6 to 12 days five guinea pigs of the first series developed fever of one to three days' duration, the other animals of this series remaining afebrile.

Of the second group of ten guinea pigs two developed fever: one after 15 days (40°.1 C.) while the other responded with several febrile attacks each of one day duration.

Spleen passages were made from the first series of guinea pigs injected with the tick filtrate. Among the various types of fever observed were those of one day duration sometimes followed by relapses and very similar to the reactions of the 1943 series. The pathological changes were also very similar to those of 1943, with predominant lesions in the lungs in form of disseminated minute petechial or hemorrhagic areas. The histopathology revealed extravasation of blood, as well as perivascular and peribronchial infiltrations. The spleen was usually slightly or moderately enlarged but in some guinea pigs it was found 2–3 times normal. The adrenals were in many cases injected and swollen. In addition to these findings which correspond to our previous records in some infected guinea pigs, clear or opalescent ascitic fluid was found, either scanty or in a moderate quantity. Bacteriological tests in aerobic and anerobic conditions gave negative results. Direct examinations of tissue smears stained with Macchiavello and of sections stained with Giemsa revealed the presence of rickettsiae as previously described (Anigstein and Bader, 1943). This strain was carried in eight passages when it became contaminated by an intercurrent infection and was discarded.

Another batch of 600 adult ticks was then examined. The unfiltered suspension was injected into 5 guinea pigs, the filtrate (Berkefeld "N") was passed to 6 guinea pigs. Three of the latter group responded with high fevers after 3, 5, and 11 days' incubation, the others remaining afebrile. In spite of definite febrile reactions, pathological lesions and the presence of rickettsiae attempts to maintain this strain in guinea pigs failed. Better results were obtained with the next series of

guinea pigs inoculated with the unfiltered tick suspension. The infection was successfully carried by transfers to the ninth generation (Sept. 8, 1944) when the bacteriologically sterile material has been lyophilized. Generally speaking about 50 per cent of passage guinea pigs showed fever of moderate or high intensity after an incubation of from 5–15 days. The mortality rate was practically nil while the pathological lesions were of the type described above. Microscopic examination of the organs in smears and sections fully confirmed our previous observations. Here again "inclusion bodies" and minute rod shaped or coccoid rickettsiae were observed in large mononuclear cells of various organs particularly in lungs. They stained red with Macchiavello and purplish red with Giemsa. In lung sections the rickettsiae containing cells are located chiefly around the bronchi in peribronchial inflammatory foci.

In view of the apparent similarity between the disease of guinea pigs infected with the rickettsial strain of 1944 (BT_2) and those infected with the 1943 strain (BT_1) it was of interest to compare both series by immunological tests. For this purpose 16 guinea pigs after recovery from the infection with BT_2 were reinoculated with BT_1 in addition to ten normal controls. Of the 16 test animals all but one remained afebrile during 17 days' observation, thus showing immunity, while of the 10 controls 2 died, 6 reacted with sharp fevers and 2 remained afebrile. Besides, 7 guinea pigs were added which several months previously were infected with the rickettsial organism originating from the tick *Rhipicephalus sanguineus*. All seven animals challenged with the same BT_1 strain remained completely afebrile.

Conclusions

1. Two rickettsial strains were recovered in summer, 1944, from the tick *Amblyomma americanum* of Camp Bullis, Texas.

2. The symptomatology and pathology of the infection in guinea pigs as well as the characteristics of the rickettsiae in the tissues correspond to previous findings of the reporters (Anigstein and Bader, 1943).

3. One of the newly recovered strains from *A. americanum* (BT_2) proved immunologically identical with the Bullis fever rickettsia (BT_1) isolated by the reporters in 1943.

4. The result of experiments on human volunteers furnish further evidence of the specificity of the isolated rickettsia for Bullis fever.

5. Intracytoplasmic inclusion bodies associated with the rickettsia of Bullis fever are described. It is possible that these inclusion bodies also observed in other rickettsiosis represent a biological phase of rickettsiae.

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Items of Possible Interest to Our Friends

AUGUST, 1944

1. About Books: Worthy of being bound separately as a book is the May, 1944, issue of the *Journal of Nervous and Mental Diseases*, dedicated by his California colleagues to Howard Naffziger on his 60th birthday; from Roy Abbott to Robt. Wartenberg, the 49 articles are excellent, with Frank Hinman's *Euthanasia* especially courageous and philosophical, and K. F. Meyer's analysis of the blood-brain barrier especially informative. Columbia Press, N.Y., publishes F. Schrader's *Mitosis* (1944, $2). B. P. Babkin's *Secretory Mechanism of the Digestive Glands* is a must (Hoeber, N.Y., 1944, $12.75). G. F. Gause's *Optical Activity and Living Matter* appears as No. 2 of B. J. Lujet's items on general physiology (Biodynamica, Normandy, Missouri, $2.75). W. Goldring and H. Chasis offer *Hypertension and Hypertensive Disease* (Commonwealth Fund, N.Y., 1944, $3.50). J. L. T. Appleton revises his *Bacterial Infection in Dental Practice* (Lea & Febiger, Phila., 1944, $7). The F. A. Gibbs issue an *Atlas of Electroencephalography* (Addison, Cambridge, Mass., 1944, $8). C. C. Thomas's stimulating list includes S. L. Osborne and H. J. Holmquest's *Technic of Electrotherapy;* J. A. Reyniers' *Micrurgical and Germ-free Methods*, and F. J. Sladen's *Psychiatry and the War* (Springfield, Ill., 1944, $7.50, $5 and $5). F. R. Lillie properly writes account of *The Woods Hole Marine Biological Laboratory* (Univ. Chicago Press, 1944, $4). Henry Schuman of New York plans to publish T. E. Keys' excellent *History of Anesthesia* appropriately for the approximate centennial.

2. Antibiotics: Merck & Co.'s mimeographed brochure (127 pp.) on penicillin is most comprehensive summary to date (303 references). H. J. Robinson's doctoral thesis under S. Waksman at Rutgers should be published for wide distribution: *Toxicological, Bacteriological, and Pharmacological Properties of Antimicrobial Agents Produced by Soil Micro-organisms* (New Brunswick, 1943). R. D. Hatchkiss well reviews information on gramacidin, tyrocidin and tyrothrycin (*Advances in Enzymology*, 4:201, 1944). H. J. Robinson & Co. propose streptothricin for infected wounds and burns (*Science*, 99:540, June 30, 1944). V. Bryson & Co. suggest aerosolization of penicillin solutions for treating infections of the respiratory tract (*Science*, 100:33, July 14, 1944).

3. Cancer: M. Juhn describes possible diagnostic use of feather germ reaction in brown leghorns to urines from cancer patients (*Arch. Path.*, 37:383, 1944). U. R. Potter offers plausible account of energy transformations in relation to cancer (*Advances in Enzymology*, 4:201, 1944). The M. Silberbergs suggest 3,4 benzpyrene as possibly useful in wound repair (*Amer. J. Path.*, 20:809, 1944).

4. CHEMOTHERAPY: H. McIlwain opens series on biochemical characterization of chemotherapeutic action with careful analysis of pantoyltaurine growth inhibition (*Bio-Chem. J.* 38:20, 1944). T. E. Lowe and H. O. Lancaster admit gentian violet helpful if not specific in treating strongyloidiasis (*Med. J. Austral.*, 1:429, May 13, 1944). D. I. Macht describes important detoxifying properties of heparin (*South. Med. J.*, 37:402, 1944).

5. IN ADDITION: K. W. Thompson's exhaustive study on relation of dermatomycosis to leg ulcers finally appears (*Yale J. Biol. Med.*, 16:665, 1944). U. S. v. Euler of Stockholm finds nicotine-like acting base in urine which he concludes is piperidine (*Nature*, 154: 17, July 1, 1944). C. de v. Bevan gives helpful hints for preparation of rickettsiae vaccines (*S. Afr. J. Med. Sci.*, 9:1, 1944). T. C. Hall and H. Lehmann find calcium peptone powder useful for increasing calcium absorption in humans (*Bio-Chem. J.* 38:117, 1944). A. Hemingway and E. Neil well survey different methods of artificial repsiration (*Brit. Med. J.*, 1:833, June 24, 1944). R. Elman concludes that nitrogen balance may be maintained by intravenous protein hydrolysates (*Physiol. Rev.*, 24:372, 1944).

6. HISTORICAL: Congratulations to the *New Orleans Medical and Surgical Journal* on its centennial. A. A. Moll's *Aesculapius in Latin America* could be muchly improved (Saunders, Phila., 1944, $7). Supplements to *Bull. Hist. Med.* include L. Edelstein's commentary on the Hippocratic Oath and W. Pagel's discussion of the religious and philosophical aspects of Van Helmont's Science and Medicine. M. Shimkin reports on medical education in the Soviet Union (*Amer. Rev. Soc. Med.*, 1:465, 1944).

SEPTEMBER, 1944

1. BOOKWARD Ho!: Educational issue J.A.M.A. (Aug. 19, 1944, Vol. 125, No. 16) always runs ads of hot medic volumes, but it misses a few: A.A.A.S. symposia, such as Aerobiology, Chemical Control of Insects, Tuberculosis and Leprosy, Malaria, Mental Health, The Cell and Protoplasm, Relapsing Fever, Fluorine and Dental Health, Surface Chemistry, and Blood, Heart and Circulation (A.A.A.S., Smithsonian Institution, Washington 25, for $3 to $4 each); various University Press publications on medicine, and medical society reports. Maybe some of these outfits should advertise in the Journal? Did you note J. S. Simmons & Co.'s *Global Epidemiology* (Lippincott, Phila., 1944, $7)? Or R. L. Pullen and Tulane's *Medical Diagnosis* (Saunders, Phila., 1944, $10)? Or O. Glasser & Co.'s *Physical Foundations of Radiology* (Hoeber, N.Y., 1944, $5)? Or F. C. Zapffe's series for medical students (Hoeber, N.Y., 1944, including M. Everett's *Biochemistry* and C. Thienes' *Pharmacology*)? Or K. Judovich and S. Bates, *Segmental Neuralgia in Painful Syndromes* (F. A. Davis, Phila., 1944, $5)? Or T. Gordon's *Romance of Medicine* (Davis, Phila., 1944, $5)? Or D. Bispham's *Malaria* (Williams & Wilkins, Balt., 1944, $3.50)? Or A. R. Rich's *Pathogenesis of Tuberculosis* (Thomas, Springfield, Ill., 1944, $10.50)? Or E. C. Rosenow's *Poliomyelitis* (*Internat. Bull. Med. Res.*, N.Y., 1944)? Or W. H. Gantt's *Experimental Basis for Neurotic Behavior*

(Psychosomatic Med. Mon., N.Y., 1944, $4.50)? Or the 1944 *New and Non-Official Remedies* (A.M.A., Chicago, 1944, $1.50)? Or *Science in Soviet Russia* (Cattell Press, Lancaster, 1944, $1.50)? Or Volume Five of J. Alexander's *Colloid Chemistry* (Reinhold, N.Y., 1944, $20)? Mimeod, but in book class are J. A. Phalen's *Blood Plasma Program* and J. J. Waring's *Spontaneous Pneumothorax* (Office Med. Info., Nat. Res. Counc., Washington, 1944, free). P. C. Bucy edits *Precentral Motor Cortex* (Univ. Illinois, Urbana, 1944), with Fulton foreword and fine contributions.

2. THIOURACIL IN TOXIC GOITER: E. B. Astwood's full summary appears (*J. Clin. Endocrin.*, 4:229, 1944). In clinical survey by T. H. McGavack & Co. it appears that 10 per cent of treated patients show toxic reactions (*ibid.*, p. 249). A. H. Meyer notes granulocytopenia after recommended dosage, with recovery after stopping drug and using pentanucleatids (*Calif. West. Med.*, 61:55, 1944).

3. INSECTICIDES: W. A. L. David & P. Bracey show that activation of pyrethrins in fly sprays by sesame oil, lubricating oil, or butylundecyleneamides is caused by increased persistence of droplets (*Nature*, 153:594, May 13, 1944). R. D. Lillie and M. I. Smith offer important report on toxicity of D.D.T. (*Pub. Health Rep.*, 59:979, 984, July 28, 1944). This is amplified in issue of August 4 with notes by A. A. Nelson & Co. Health hazard involved by oral or skin absorption—no data on inhalation in fly sprays—with possible hyaline and fatty degeneration of the liver, and with nervous symptoms. Ingested thiamin is NO mosquito repellent, say C. S. Wilson & Co. (*Science*, 100: 147, Aug. 18, 1944) in refutation of W. R. Shannon (*Minnesota Med.*, 26:799, 1943).

4. ANTIBIOTICS: S. A. Waksman & Co. demonstrate control of gram-negative infections by streptomycin (*Science*, 100:103, Aug. 4, 1944). D. H. Rosenberg and J. C. Sylvester report penicillin rapidly penetrates meninges and that IV or IM administration should be effective in meningitis (*Science*, 100:132, Aug. 11, 1944). J. Brunel reminds us that many others noted antibiotic action before Fleming (*Rev. Canad. Biol.*, 3:333, 1944).

5. THUS & SO: In the July, 1944, Gastroenterology, dedicated to Ajax Carlson, appears W. Alvarez's discussion on heartburn. F. H. J. Figge & Co. show excessive porphyrin excretion by UV fluorescence and suggest relation to cancer susceptibility (*Cancer Res.*, 4:465–486, 1944). E. L. Way and L. K. Chan note low toxicity and high trypanicidal action of arsenical sulfonamide (*J. Pharmacol. Exp. Therap.*, 81:278, 1944). A. Albert & Co. of Sydney note antistaphylococcal action of mapharsen (*Nature*, 153:712, June 10, 1944). J. Sacks show glucose absorption by muscle occurs by formation of hexaphosphate on cell membrane (*Amer. J. Physiol.*, 142:145, 1944). R. W. Raven describes effectiveness of dusting proflavine powder in wounds (*Lancet*, 2:73, July 15, 1944). J. H. Ridout & Co. find that alloxan causes hypoglycemia by killing islet cells, with resulting insulin leeching into blood (*Science*, 100:57, July 21, 1944). I. Aird discusses military surgery in geographical perspective (*Edin. Med. J.*, 51:184, 1944). J. F. Rinehart's ideas on salt metabolism in polio are in Naffziger volume (*J. Nerv. Ment. Dis.*, 99:825, 1944).

OCTOBER, 1944

1. HISTORICAL: On December 11, 1844, Horace Wells, of Hartford, former dental partner of W. T. G. Morton, had a tooth extracted without pain by Dr. John Riggs, using N_2O prepared by G. Q. Colton; appropriate for the centennial is the well illustrated "Life and Letters of Horace Wells," by W. H. Archer (*J. Amer. Coll. Dentists*, 11:81–210, 1944). Preview of J. B. DeC. M. Saunders and C. D. O'Malley's translation of the Vesalius *Fabrica* (1543) appears (*ibid.*, 211–218). Their translation and annotation of the *China Root* (1546) should appear soon. F. J. Cole offers a *History of Comparative Anatomy from Aristotle to 18th Century* (Macmillan, London, 1944). H. Bailey and W. J. Bishop publish well illustrated *Notable Names in Medicine and Surgery* (H. K. Lewis, London, 1944). I. Galdston discusses Descartes and modern psychiatric thought (*Isis*, 35:118, 1944). J. W. Wilson reviews cellular tissue and the dawn of the cell theory (*ibid.*, 168). Why not buy some of the classics of medicine, as suggested so wistfully by H. Sigerist (*Bull. Hist. Med.*, 16:1, 1944)? Congratulations to *La Juventud Medica* of Guatemala on its semicentennial.

2. BLOOD SUBSTITUTES: F. S. Robscheit-Robbins & Co. discuss usefulness and toxicity of gelatine as a plasma protein substitute (*J. Exp. Med.*, 80:145, 1944). A. Wormall discusses the non-antigenicity of gelatine (*Nature*, 154:332, Sept. 9, 1944). G. Riedel and K. Zipf suggest "periston" (2½ per cent polyvinyl-pyrrolidon in buffered Ringer's sol.) IV as useful blood substitute in hemorrhagic shock (*Arch. Exp. Path. Pharmak.*, 203: 25, 1944).

3. CHEMOTHERAPY: P. Ellinger & Co. find sulfonamide sterilization of gut interferes with production of nicotinamide by intestinal flora, possibly causing deficiency symptoms (*Nature*, 154:270, Aug. 26, 1944). J. Ohnysty and W. D. Wolfson recommend 10 Gms. potassium bicarbonate daily as adjunct to sulfonamide therapy in pneumonia complicating cardiac decompensation (*New Eng. J. Med.*, 231:381, Sept. 14, 1944). M. A. Schnither and C. C. Lenhoff report that 30 Gms. urea daily with sulfonamides will break most sulfonamide resistance in gonorrhea (*J. Lab. Clin. Med.*, 29: 889, 1944).

4. ANTIBIOTICS: H. W. Florey & Co. offer brief symposium on penicillin (*Brit. Med. J.* 2:169–179, Aug. 5, 1944). O. Roberts and D. Murphy recommend penicillin agar for local application to infected areas (*Irish J. Med. Sci.*, 6th ser., 223:225, 1944). I. W. J. McAdan & Co. suggest 3-hour IM inj. of 25,000 units in 2 cc. for emergency or ambulatory patients—otherwise continuous IM infusion 100,000 units in 100 cc. per day (*Lancet*, 2:336, Sept. 9, 1944). J. Unger describes penicillinase from B. subtilis (*Nature*, 154:236, Aug. 19, 1944).

5. BOOKS: T. H. Howell offers *Old Age: Practical Points in Geriatrics* (H. K. Lewis, London, 1944). G. Draper & Co. issue *Human Constitution in Clinical Medicine* (P. B. Hoeber, N.Y., 1944). F. W. Jones follows his fine *Principles of Anatomy as Seen in the Hand* with his equally important

Structure and Function as Seen in the Foot (Bailliere, Tindall & Cox, London, 1944). D. Hunter's 1942 Croonian Lectures on *Industrial Toxicology* finally appear (Oxford Press, 1944). S. C. Shanks edits 3 vol. *Textbook of X-Ray Diagnosis* (H. K. Lewis, London, 1944). R. R. Foote presents *Varicose Veins, Hemorrhoids and Other Conditions: Their Treatment by Injection* (H. K. Lewis, London, 1944). S. F. Markham discusses *Climate and the Energy of Nations* (Oxford Press, 1944). W. N. Bispham describes *Malaria: Its Diagnosis, Treatment and Prophylaxis* (Williams & Wilkins, Balt., 1944). A. A. Brill notes Freud's Contribution to Psychiatry (Norton, N.Y., 1944).

6. OTHERWISE: J. O. Parnas makes fine review of biologic catalysis (*Amer. Rev. Soviet Med.*, 1:485, 1944). P. D. Lamson thinks "biotrepy" is the golden egged goose (*Sci. Monthly*, 59:215, 1944). J. P. Greenstein & Co. begin important chemical study of human cancer (*J. Nat. Cancer Inst.*, 5:55, 1944). W. F. Friedewald and P. Rous survey initiating and promoting elements in tumor production (*J. Exp. Med.*, 80:101, 1944). H. C. de Souza-Araujo prepares leprosy antigens ("leprolins") for diagnosis and treatment (*Mem. Inst. Oswaldo Cruz*, 39:349, 1943; 40:101, 1944). Note excellent symposium on peripheral vascular disorders, low temperature injury, and traumatic arterial spasm (*Brit. Med. Bull.*, 2:136, 1944). E. J. Carey continues fine work on secretion of motor end-plates, showing polio effects (*Amer. J. Path.*, 20:961, 1944).

NOVEMBER, 1944

1. INTERESTING AND AMUSING: Be sure to read G. W. Corner's *Ourselves Unborn: An Embryologist's Essay on Man* (Yale Press, New Haven, Conn., 1944, $3), the best Terry Lecture in years, wise, witty and well done. Enjoy A. E. Hertzler's *Ventures in Science of a Country Surgeon* (privately printed, Halstead, Kansas, 1944), clear, colorful and courageous, with Ray Allen's foreword stressing Hertzler's thesis that the good doctor is a student always. Get R. M. Wilson's *British Medicine* (Britain in Pictures series, Hastings House, N.Y., 1944, $1.25) if for nothing else than its fine illustrations. Note National Music Council (338 W. 89, N.Y. 24) reports on use of music in hospitals for mental and nervous diseases.

2. TO THINK ABOUT: Excellent recommendations for the *National Medical Library* in survey of Army Medical Library by K. D. Metcalf & Co. (Am. Lib. Asso., Chicago, 1944). Q. Wright's homily on freedom in universities (*A.A.U.P. Bull.*, 30: 167, 1944) neglects to mention significance of personal responsibility in justifying freedom. H. T. Houf discusses the ideal University president, noting importance of unselfishness (*ibid.*, p. 277). J. K. Wright reports on human nature in science (*Science*, 100:299, Oct. 6, 1944). Nursing Information Bureau of American Nurses' Asso. issues *Facts About Nursing*, 1944 (1790 Broadway, N.Y. 19). Better write for a copy!

3. BOOKS TO GET: Edwards Bros., Ann Arbor, Mich., will issue the S. C. Brooks' long awaited monograph on permeability, about which they had

such trouble abroad and at home. Also from Edwards Bros.: H. Buscher on pathology and therapy of chemical warfare injuries ($4); C. A. O. Franz on military surgery ($13); K. Hinsberg's Geschwulstproblem in Chemie and Physiologie ($8.25), and F. Kauffmann on the bacteriology of the salmonella organisms ($7). For popular use it's hard to beat E. W. Hayes' *Tuberculosis As It Comes and Goes* (privately printed, Monrovia, Calif., 1943). G. Hosford recommends S. A. Fox's *Your Eyes* (Knopf, N.Y., 1944, $3). Genial Manchester historian (medical), E. M. Brockbank offers neat biography of John Dalton and account of his theory of colour vision (Manchester Univ. Press, 1944, $2). R. A. Moore writes a new *Pathology* (Saunders, Phila., 1944). A. R. Rich's *Pathogenesis of Tuberculosis* looks like a honey (C. C. Thomas, Springfield, Ill., 1944, $10.50). E. F. Burton offers *The Electron Microscope* (Reinhold, N.Y., 1944, $3.85). Harvey Cushing's Visit to *Le Puy-en-Velay* appears with notes by John Fulton (Rowfant Club, Cleveland 15, $8). Get R. J. Behan's *Pain: Its Origin, Conduction, Perception and Diagnos-Significance* (Appleton, N.Y., 1944). Important is W. R. Bloor's *Biochemistry of the Fatty Acids* (Reinhold, N.Y., 1944, $6). R. A. Sawyer's *Experimental Spectroscopy* looks tops (Prentice-Hall, N.Y., 1944, $3.75). W. W. Babcock offers *Principles and Practice of Surgery* (Lea & Febiger, Phila., 1944, $12). R. S. Harris and K. V. Thimann survey *Vitamins and Hormones* (Academic Press, N.Y., 1944, $6.80). G. Seifer's *Virus Diseases in Man, Animal and Plant* is OK (Philosophical Lib., N.Y., 1944, $5). Interesting is W. F. Norwood's *Medical Education in the U. S. before the Civil War* (Univ. Penn. Press, Phila., 1944, $6). Outstanding is S. Bunnell's *Surgery of the Hand* (Lippincott, Phila., 1944, $12). See F. D. Murphy's *Acute Medical Disorders* (Davis, Phila., 1944, $6). J. Dollard & Co. (Yale) study *Frustration and Aggression* (Kegan Paul, Lond., 1944, $3). L. R. Broster undertakes *A Study in the Surgery of Sex* (Heineman, Lond., 1944, $5).

4. ANTIBIOTICS: E. S. Duthie describes production of penicillinase by organisms of subtilis group (*Brit. J. Exp. Path.*, 25:96, 1944). G. Soo Hoo and R. J. Schnitzer note that penicillin synergizes with sulfonamides but not with acridines (*Arch. Biochem.*, 5:99, 1944). M. R. Lewis observes that while impure penicillin may damage sarcomatous cells, pure penicillin will not (*Science*, 100:314, Oct. 6, 1944). A. E. Francis & Co. find definitely that patulin has no value in common cold (*Lancet*, 2:370, Sept. 16, 1944). J. W. Bigger notes that penicillin is inactivated by blood and serum (*Lancet*, 2:400, Sept. 24, 1944). C. J. Cavallito and J. H. Bailey report that cysteine and esters, but not other SH cmpds, inactivate penicillin, citrinin, clavacin, pyocyanine, and new antibiotic from allium sativum (*Science*, 100:390, Oct. 27, 1944). Note on same page G. Schwartzman's cellophane method for growing penicillin.

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